Docket No.: ATX-007CP4DV12
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
John J. Harrington *et al.*

Application No.: 09/484,331 Confirmation No.: 9576

Filed: January 18, 2000 Art Unit: 1632

For: COMPOSITIONS AND METHODS FOR NON-TARGETED ACTIVATION OF ENDOGENOUS GENES Examiner: WOITACH, Joseph T.

## APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants file this brief months more than two months from the filing of the Notice of Appeal filed for this case on April 5, 2005, and in furtherance of said Notice of Appeal.

This appeal brief is accompanied by a four-month petition for extension of time for filing this brief and the requisite fees.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:



## I. Real Party in Interest

The real party of interest in this appeal is:

Athersys, Inc.

## II. Related Appeals, Interferences, and Judicial Proceedings

There are no other appeals, interferences or judicial proceedings known to appellant which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

## III. Status of Claims

A. Total Number of Claims in Application

There are two (2) claims pending in the application.

B. Current Status of Claims

1. Claims canceled: 1-68
2. Claims pending: 69 and 70
3. Claims allowed: none
4. Claims rejected: 69 and 70

C. Claims on Appeal

The claims on appeal are claims 69 and 70.

## IV. Status of Amendments

Applicant filed an Amendment After Final on January 3, 2005. The Examiner issued an Advisory Action mailed February 16, 2005. In the Advisory Action, the Examiner indicated that Applicants' Amendment After Final would be entered.

Accordingly, the claims enclosed herein as Appendix A reflect the claims as pending.

## V. Summary of Invention

The instant invention is related to a method of drug discovery comprising, (a) integrating a vector comprising a promoter into the genome of one or more eukaryotic cells by non-homologous recombination, where the promoter activates expression of an endogenous gene in these cells; (b) culturing the cell(s) from step (a) under conditions favoring expression of the activated gene, thereby producing a gene product of the activated gene; (c) screening the cell(s) from step (b) for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by the activated gene; (d) treating the cell(s) from step (c) with one or more test compounds; and (e) determining the ability of the test compounds to interact with a product of the desired activated gene or to affect the desired phenotype.

## VI. Grounds of Rejection to be Reviewed on Appeal

Claims 69 and 70 stand rejected under 35 U.S.C. §112, first paragraph, on the grounds that they fail to comply with the written description requirement for reasons of record set forth in the previous non-final Office Action of December 23, 2003.

Claims 69 and 70 also stand rejected under 35 U.S.C. §112, first paragraph, on the grounds that they fail to comply with the enablement requirement for reasons of record set forth in the Office Action of December 23, 2003.

## VII. Argument

### A. Written Description Rejection of Claims 68 and 69 under 35 U.S.C. §112, First Paragraph

The basis for the written description rejection is the Examiner's opinion that generally disclosing drug discovery with RAGE technology does not reasonably convey the *specific* steps in the claims. The Examiner frames the issue as follows: "how could the specification lead an artisan to the specific steps recited in the claim? In other words, how would an artisan know what specific steps were contemplated by the applicants at the time of the invention." Final Office Action, October 05, 2004, page 5. The Advisory Office Action restates the same point. Advisory Office Action, February 16, 2005, page 2.

This specific issue has been addressed in an expert Declaration in the file history. Up to the present, however, this Declaration has not been considered *for its substance on this very issue.*

#### 1. The Dhanoa Declaration Has Not Been Considered for the Relevant Issue

The Declaration of Dr. Dale Dhanoa,[1] a qualified expert in the field of drug discovery, was submitted with Appellants' Response dated July 10, 2003. Based on detailed scientific reasoning Dr. Dhanoa reached the following conclusion:

> Based on my reading of the patent application, therefore, it is my opinion that the person of ordinary skill in the field of drug discovery, reading this application on or about the filing date of September 26, 1997, would have realized that the Applicants, by mentioning the drug discovery process as they did, implicitly were

[1] Reference 2 in the Evidence Appendix.

> describing the drug discovery method in claims 62-69, copy attached.

Dhanoa Declaration page 9.

This Declaration was submitted specifically to address the issue of whether the steps in the claims were reasonably conveyed to the person of ordinary skill in the art. The steps currently at issue were in then-pending claims 62-69, which the Declaration considered. Therefore, the Declaration applies to the current claims as well. A copy of the then-pending claims 62-69 is attached to the Declaration, Reference 2, in the Evidence Appendix.

Appellants respectfully submit that the person of ordinary skill in the art would have understood from the term "drug discovery" steps that MUST be used for drug discovery with the RAGE-activated cells. Thus, the steps are inherent and would have been recognized immediately by one of ordinary skill in the drug discovery industry. Support need not be explicit as long as the specification reasonably conveys the claimed steps. If by the term "drug discovery" the person of ordinary skill would have recognized how this is conventionally done, then the claim is adequately described so that the artisan can practice the method as claimed.

This issue has been addressed in two expert Declarations in the file history. Up to the present, however, the Bennani Declaration has been dismissed without substantive reason. And the Dhanoa Declaration has not even been considered for its substance on this issue.

The Dhanoa Declaration addressed only the question of whether the claimed steps would have been implicitly disclosed to the person of ordinary skill in the art reading the specification. The Dhanoa Declaration was not concerned with the adequacy of written description of the compounds. Therefore, the Examiner's statement is factually incorrect.

Appellants clearly stated why they submitted the Dhanoa Declaration in their Response dated July 10, 2003. Briefly, during an interview held on May 16, 2003, Examiner Reynolds explained that, based on her review of the text directed to drug discovery in the specification, the specification did not describe the steps of compound testing on the cells, i.e. the issue at hand. The Declaration was submitted to address this issue alone. See page 14 of Appellants' Response dated July 10, 2003. There should be no confusion, therefore, about why the Declaration was presented and no reason to believe that it addresses the issue of adequate description of compounds.

2. The Dhanoa Declaration Has Been Considered For An Issue It Does Not Address

The issue of adequacy of description of the compounds recited in the claims was raised in the non-final Office Action dated October 25, 2001. There, the Examiner stated that compounds are critical to practice the claimed invention and structures must be described. No specific compounds were described in the specification. That clearly was the sole basis for the rejection.

In Appellants' Response dated April 25, 2002, Appellants asserted that it was the policy of the PTO to allow drug screening claims without a description of the compounds because the PTO realized that random compounds were routinely tested. Appellants cited a slide presentation to this effect given by Brian Stanton at a Biotechnology Partnership meeting. See pages 7, 8, and 10 of Appellants' April 25, 2002 Response. Appellants also submitted an expert Declaration by Dr. Youssef L. Bennani, Director of Medicinal Chemistry at Athersys, Inc., explaining scientifically why, for compound testing, the structure of the test compound was not critical (page 3 of the Declaration).[2]

[2] Reference 1 in the Evidence Appendix.

In the final Office Action dated January 13, 2003, the rejection was maintained for reasons of record. In a subsequent interview (May 16, 2003) with Appellants and the Examiner, the Examiner's supervisor (Deborah Reynolds), and Brian Stanton, Mr. Stanton indicated that if indeed the claims were generic drug discovery claims then the compounds need not be described. In the subsequent (Advisory) Action of August 5, 2003, the rejection was withdrawn *on the basis of the Dhanoa Declaration*. Because the Dhanoa Declaration did not address compound description, Appellants assumed this was an inadvertent erroneous statement.

The basic point is that the Dhanoa Declaration cannot have been considered on the issue of written description for compounds since it didn't address this issue. Thus, the Declaration has not been considered for its evidence on the pertinent issue. Because the Declaration has not been considered for the correct issue, the rejection is improperly supported.

3. Written Description Can Be Inherent

The term "drug discovery" was well-understood in the art. As two expert Declarations stated, an artisan would have known what steps the Appellants had in mind when they referred to "drug discovery." The specifics of these steps need not have been explicitly stated in the application to be used in the claims. As the CCPA stated, "the invention claimed does not have to be described in *ipsis verbis* to satisfy the description requirement of §112." *In re Lukach*, 58 C.C.P.A. 1233, 1235 (CCPA, 1971). "The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570,

1575, 227 U.S.P.Q. (BNA) 177, 179 (Fed. Cir. 1985). According to the Dhanoa Declaration, this applies to the present case.

4. The Dhanoa and Bennani Declarations Demonstrate that the Specification Inherently Discloses the Recited Steps

The Dhanoa Declaration squarely addresses the issue of whether the specification conveys to the artisan the steps recited in the claims. As the Dhanoa Declaration states, an artisan would have realized that, by disclosing "drug discovery," Appellants implicitly described the claimed drug discovery method. Having described the process of drug discovery, Dr. Dhanoa stated: "...the cited passages (referring to drug discovery), within the full context of the application, would have indicated to me that a compound could be tested against a RAGE cell with an activated gene of interest to determine if the compound affects the gene of interest or phenotype of interest." Dhanoa Declaration, page 9. The Examiner provides no evidence contradicting this statement.

Furthermore, the Bennani Declaration states that, "[I]n my experience, the person of ordinary skill in the art (i.e., drug discovery) would immediately recognize the claimed method in the term "drug discovery" and would know how to use the RAGE-activated cells for drug discovery, including the well-known and fundamental steps used in such research field." Bennani Declaration, page 5. Again, the Examiner provides no evidence contradicting this statement.

5. The Dhanoa Declaration Impermissibly Dismissed as the Examiner Has Not Met Burden

First, the Declaration was not considered for what it addresses. Therefore, it has not been properly considered on the relevant issue. Accordingly, the rejection is, at best, incomplete.

Next, the Declaration was dismissed for impermissible reasons. There is no scientific or logical rebuttal of the evidence presented in the Declaration. The Examiner merely repeated the same unsubstantiated position as follows.

> How could the specification lead an artisan to the specific steps recited in the claim? In other words, how would an artisan know what specific steps were contemplated by the Applicants at the time of the invention. And the declaration cannot address this issue.

Final Office Action dated October 5, 2004, page 5.

Similarly, in the Advisory Office Action dated February 16, 2005, a new Examiner stated that "[T]he declaration of Bennani and Dhanoa have been fully considered, and do not appear to have been ignored or dismissed. As indicated previously, it has been found that the declarations fail to provide any objective evidence for the conclusions regarding the specifically claimed invention." (*sic*). Advisory Office Action, page 2.

As Appellants demonstrated, neither declaration was considered for the relevant issue of written description. Unsubstantiated statements made by the Examiners in the Office Actions fail to constitute scientific or logical reasons to rebut the evidence presented in the Declaration. Contrary to the Examiner's statement that "the declaration cannot address this issue," the Declaration can and does address this issue.

Accordingly, the Examiners have impermissibly substituted their opinions for an expert's opinion which was based on sound scientific reasons about what the ordinary skilled artisan would have recognized from the Appellants' specification.

6. Appellants Do Not Attempt to Satisfy Written Description Requirement Through Obviousness

In the Advisory Office Action, February 16, 2005, the new Examiner raises a new legal issue. He states that Appellants are attempting to satisfy the written description

requirement through obviousness. Advisory Office Action, p.2.The Examiner cites *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398, at 1405 (Fed. Cir. 1997) for the proposition that "a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement."

Appellants do not dispute this proposition. However, Appellants have not attempted to satisfy the written description requirement through obviousness. Appellants submitted and proved by expert Declarations that the specification sufficiently conveys the claimed invention to the person of ordinary skill. The Declarations demonstrate that a person of ordinary skill in the art reading the Appellants' specifications would recognize the specific claimed steps as inherent in the term "drug discovery."

Therefore, the Examiner's reliance on *University of California* is misplaced.

7. The Examiner Erroneously States That the Term "Drug Discovery" Was Added to Overcome §102 Rejections

In the Advisory Office Action dated February 16, 2005, the new Examiner states, "It is noted that the claims have been amended during prosecution to address rejections made under 35 USC §102. Neither declaration addresses why the statement of use for "drug discovery" allows one to amend claims to differentiate it from the prior art." Advisory Office Action, page 2. This statement is factually incorrect. The term "drug discovery" was in the original claims and was not added to overcome any rejection under §102. In fact, claim 69 was never rejected under §102.

Claim 69 is a combination of independent claim 62 and its dependent claim 68. The limitations of claim 68 were incorporated into claim 62 to arrive at claim 69. In the non-final Office Action of October 25, 2001 (page 11) claim 62 was rejected under §102. Claim 68

was not rejected. Therefore, current claim 69 was never subject to a rejection under §102. See Appellants' Response dated April 25, 2002, page 21 (para spanning pages 21-22).

8. The Examiner Improperly Challenged the Mental Process of Declarant

In the Final Office Action of October 05, 2004, the Examiner states that Dr. Dhanoa reached the wrong conclusion because of the *order* in which he *may* have reviewed the file history.

> Furthermore, from the declaration it is also unclear whether Dr. Dhanoa saw the claims and the rejection first before seeing the specification language because this would result in Dr. Dhanoa analyzing the specification keeping in mind the claim language. Office Action, p.4, line 5 from below.

The Examiner cites no case law or administrative regulations which specify how an expert is supposed to assess the facts, and, specifically, which would regulate whether or not an expert may see the disputed claims and the rejection before rendering his or her opinion. Appellants are unaware of any case law or administrative regulations where speculation about how an analysis was done adequately meets the burden for an Examiner to rebut an expert declarant. Even if Dr. Dhanoa's review was in the order suggested by the Examiner, Appellants are still unaware of any precedent showing that this type of review would be sufficient for an Examiner to meet the burden of rebutting an expert declarant. It must be presumed that an expert in the field can review the file history in any sequence they choose and still reach an objective conclusion based on sound scientific evidence or reasoning. The Examiner has not shown that Dr. Dhanoa failed to reach such an objective conclusion.

9. Dr. Dhanoa Discussed Patent Application 08/941,223

In the final Office Action of October 5, 2004, the Examiner focused on the fact that the Dhanoa Declaration lists **09**/941,223 as a U.S. Patent Application, instead of **08**/941,223.

The Examiner stated that "it is not clear which patent application did Dr. Dhanoa see." Office Action, page 4.

As Appellants explained in the Response of January 3, 2005, in his Declaration, Dr. Dhanoa inadvertently mistyped the application number as 09/941,223 instead of 08/941,223. However, there is no doubt which application Dr. Dhanoa reviewed. As the Examiner himself pointed out, there is no application number 09/941,223. The only application which discusses the RAGE technology, and which was filed on September 26, 1997, is application number 08/941,223.

Therefore, it is certain that Dr. Dhanoa discussed application number 08/941,223.

10. Summary Conclusion

Appellants have presented ample evidence that the specification adequately describes the specific method claimed. The scientific evidence and reasoning in the Declaration has not been challenged with scientific or logical evidence. Therefore, Dr. Dhanoa's conclusion must be accepted. It is error to dismiss the Declarant's testimony without adequately articulating the reasons why the testimony fails to overcome the determination to reject the Appellants' application. *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996); *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

With regard to the Dhanoa and Bennani Declarations, Appellants point out that they are offering factual evidence relating to drug discovery methods and the Declarants' understanding of the invention. The Federal Circuit cautioned that such factual evidence should not be dismissed lightly. *In re Alton*, at 1175.

Despite the Examiner's statements, the Dhanoa Declaration has never been properly considered for its pertinent teachings. Appellants demonstrated that the Examiner considered the Dhanoa Declaration with respect to an unrelated written description rejection,

but never considered the Dhanoa Declaration with respect to the current written description rejection. Merely stating in the Advisory Action that the declarations "fail to provide any objective evidence for the conclusions regarding the specifically claimed invention" is not enough to rebut the expert's conclusions. Therefore, the Examiner did not carry its burden of overcoming the expert's Declaration and the rejection should be reversed.

Appellants submit that the totality of the record, consisting of the Appellants' disclosure, arguments, and two Declarations by experts in the field, points to the conclusion that the specification adequately discloses the claimed method.

B. Rejection of Claims 68 and 69 under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 69 and 70 are rejected under 35 U.S.C. §112, first paragraph, on the grounds that they "fail to comply with the enablement requirement for reasons of record set forth in the previous office action of 12/23/03."

The reasons of record in the Office Action of December 23,2003, were based in part on the reasons for the rejection in the Office Action of October 25, 2001. But the reasons for rejection in the October 25, 2001 Office Action were already successfully resolved earlier in prosecution. These reasons have been resurrected and Appellants have been unable to obtain an explanation for this. The history is as follows.

In the very first Office Action, dated April 28, 2000, the claims (with substantially the same steps as the current claim 69) were rejected as not enabled because the Examiner took the position that before compounds could be selected for testing, the identity of the activated gene must be known. The Examiner believed that only then could an appropriate compound be selected. See pages 4-7 of that Office Action.

This issue was resolved in an interview with the Examiner and his supervisor, Mr. Priebe. Mr Priebe indicated that reciting the term "desired" with reference to the gene and

phenotype would resolve the issue. Accordingly, at Mr. Priebe's direction, Appellants refiled the case with the amendment. The Examiner then withdrew the rejection in its entirety (Office Action April 11, 2001).

Then, in a second non-final Office Action (the October 25, 2001 Office Action), the same claims that had been refiled were newly rejected as non-enabled, in part for the same reasons they had been rejected in the April 28, 2001 Office Action. These reasons have carried over into all of the remaining Office Actions. See the paragraph spanning pages 5-6 in the December 23, 2003 Office Action, the paragraph spanning pages 7-8 and pages 8 and 9 of the October 25, 2001 Office Action, and compare that to the April 28, 2000 Office Action, pages 4-7. It is evident that a basis for rejection that had been resolved has been improperly reinstated.

Thus, the current rejection is based in part on an issue that has already been resolved, It is not clear if that issue is the dispositive one. If it is, then because this issue has been resolved, the rejection should be withdrawn.

1. Step (e) is Enabled

The only question is whether the person of ordinary skill could have practiced each of the steps without undue burden of experimentation. The Examiner has already acknowledged that steps (b) – (d) are routine. ("While it would have been routine to culture a cell, expose it to compound (steps b-d of the claimed method), it would not have been routine to determine the ability of one or more compounds to interact with the product of the activated gene..." Office Action of December 23, 2003, page 5). See also Point 5, page 2. Accordingly, the Examiner takes the position that step (e) was not routine. However, as Appellants have explained to the Examiner, step (e) would also be routine.

2. It is Routine to Determine Whether a Test Compound Affects a Desired Activated Phenotype or Interacts with a Product of a Desired Activated Gene

As mentioned above, the Examiner's arguments were set forth also in the Office Actions dated April 28, 2000 and November 17, 2000. Appellants addressed the arguments in their responses to both of these Office Actions. Once again, in the December 23, 2003 Office Action and final Office Action of October 5, 2004, the Examiner asserts that it is necessary to know the characteristics/properties of both a gene and a test compound to determine the ability of the test compound to interact with a product of the gene. But this is scientifically incorrect within the context of the compound screening process. Appellants have explained in detail how compound testing in drug discovery is done with up to hundreds of thousands of random compounds. All that is required is an assay to detect the compound's effect on a particular gene product or phenotype. See the Bennani Declaration, page 3, for example.

Appellants underscore that the claimed methods recite a "desired gene and phenotype." Since the gene is desired, it is by definition known. And since a phenotype is "desired," it is, by definition, detectable. Since the method can be used for different known genes, characteristics/properties of the genes would differ because different known genes have different characteristics/properties. Appellants stress that knowing all characteristics and properties of a gene is not required to practice the claimed methods. All that is required is an assay for a product of that gene (or way to detect a phenotype).

The claims recite "determining the ability of said one or more test compounds to interact with a product of said desired activated gene or to affect said desired phenotype." This step implies that artisans would use available assays for a particular desired gene product or particular desired phenotype. There are many assays existing in the art for

various genes and phenotypes. If an artisan is interested in a particular gene, the artisan would use an assay available for that gene to determine the effect of various test compounds on the gene. Likewise, if an artisan wants to determine whether a test compound affects a specific phenotype, the artisan simply determines whether a test compound affects the phenotype in some way using a suitable assay.

In the Advisory Office Action dated February 16, 2005, the new Examiner states that Appellants' arguments are unconvincing because the use of an artificial promoter to express a gene would not represent something found in nature or a disease state. This is a new argument. In any event, Appellants are not sure how it is relevant to the issue. Appellants' claims are not directed to naturally-occurring expression systems or model systems of any disease states. Instead, claims are directed to "a method for drug discovery." As the Bennani Declaration explained, drug discovery typically utilizes an *in vitro* biochemical or cellular assay in which a gene or phenotype of interest is activated. The protein or the cell is treated with a large selection of "off the shelf" compounds. The compounds which affect the gene product or phenotype of interest are then further evaluated for their suitability to be drug candidates. Appellants' claims only cover the steps of this process up to identifying test compounds which have any effect on a product of a gene of interest or which affect a desired phenotype. Thus, it is not necessary to create a "model system" of a disease to practice the Appellants' invention.

In the Final Office Action, page 6, the Examiner states that it is relevant to know whether one or multiple genes affect the phenotype "since the method is for finding a drug for a certain gene." Appellants respectfully disagree. While in one embodiment of the invention the method can be used to find a drug for a certain gene, in other embodiments, the method can be used without knowing the gene (or genes) responsible for a specific

phenotype. The claims do not recite a method for finding a compound for a certain gene. Claims are directed to "a method for drug discovery" which may include both finding compounds that affect specific genes and compounds that affect specific phenotypes without reference to any specific gene.

For example, suppose that a desired phenotype is resistance to a protease inhibitor. An artisan would introduce a vector into cells, culture the cells, and screen for cells having the resistance phenotype. Then, the artisan would expose the cells having the phenotype (resistance) to various test compounds to determine if any test compound has an effect on the phenotype (resistance). Because only an effect on the phenotype (resistance) is assayed, knowledge of the gene (or genes) that cause the phenotype (resistance) is not necessary. All the artisan is interested in is whether a test compound affects the phenotype (resistance).

Thus, the Examiner's assertion on page 6 of the final Office Action that "...the method is for screening of compounds that affect gene product of a gene [sic] and not for screening of compounds that affect drug resistance" is incorrect. One would, in fact, screen for compounds that affect drug resistance if that is the desired phenotype. The method recites determining the ability of a test compound to affect a desired phenotype. Therefore, the method encompasses screening compounds which affect the desired phenotype of drug resistance irrespective of the gene or genes that cause it.

3. <u>There is No Need to Know Up Front the Structure of Test Compounds As it Relates to the Gene Product</u>

The Bennani Declaration explained that in drug discovery, an artisan would test randomly selected compounds. In the Final Office Action of October 5, 2004, the Examiner dismissed the Declaration as follows:

> Applicants arguments that an artisan could take any compound (as discussed in the declaration by Bennani) are not persuasive

> because an artisan would need to know the structure of the compound, structure of the gene product and requirements for the interaction of the compound to interact with a gene product to practice step (e). Applicants do not discuss where the specification discusses how to determine the ability of one or more compounds to interact with a product of an activated gene, which characteristics of a gene product or compound will be used in determining such.

Office Action, page 6.

The Examiner's statement does not provide sufficient evidence to rebut the statements of Dr. Bennani, which are based on his industry experience in drug discovery. As Dr. Bennani explained, in drug discovery, test compounds are typically taken "off the shelf" and are exposed to cells to assess their effect on a particular gene or a phenotype. Assays are specifically designed to be able to measure the effect of any compound on a desired gene or a phenotype.

The Examiner simply reasserts his position without any scientific rebuttal evidence. Contrary to the Examiner's statement, Dr. Bennani has shown why an artisan would not need to know the relationship between the structures of a test compound and gene product to practice step (e). Up front knowledge of "requirements" for interaction are NOT necessary and, typically, not even considered. All that is needed is an assay to determine the effect of a test compound on a particular gene's expression or on a particular phenotype. Thus, all that is necessary is a way to detect a gene product or a phenotypic screen.

4. Schemes and Diagrams Were Provided to Assist the Examiner and Are Not Necessary to Understand the Claimed Invention.

In the Final Office Action, the Examiner stated that "while applicants provide elaborate schemes and explanations, none of these are present in the specification and

therefore an artisan would not have had these descriptions for practicing the claimed invention."

Appellants provided schematic explanations showing how the invention works with a sole reason: to assist the Examiner to understand the invention. The person of ordinary skill in the art would not have needed this assistance.

Accordingly, Appellants believe that they have addressed each of the grounds of the rejection and the rejection has been overcome. Reversal of the rejection is respectfully requested.

## VIII. Claims Involved in the Appeal

A copy of the claims involved in the present appeal are attached hereto as Appendix A. As indicated above, the claims in Appendix A are the claims as pending.

## IX. Evidence

| Reference Number | Reference Title |
|---|---|
| 1 | A copy of the Bennani Declaration, submitted under 37 CFR §1.132 on April 24, 2002 along with Applicants' Amendment and Remarks, attached as Appendix B herewith. |
| 2 | A copy of the Dhanoa Declaration, submitted under 37 CFR §1.132 on July 10, 2003 along with Applicants' Amendment and Remarks, attched as Appendix C herewith. |

## X. Related Proceedings

No related proceedings are referenced in II. Above, or copies of decisions in related proceedings are not provided, hence no Appendix is included.

Appellant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. ATX-007CP4DV12 from which the undersigned is authorized to draw.

Dated: October 5, 2005

Respectfully submitted,

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# APPENDIX A

PENDING CLAIMS

69. A method for drug discovery comprising:

(a) integrating a vector, comprising a promoter, into the genome of one or more eukaryotic cells, by non-homologous recombination, wherein said promoter activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells under conditions favoring expression of said activated gene, thereby producing a gene product of said activated gene;

(c) screening said one or more cells for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by said activated gene;

(d) treating said cell, in which said desired gene is activated or in which said desired phenotype is induced, with one or more test compounds to be screened for drug activity; and

(e) determining the ability of said one or more test compounds to interact with a product of said desired activated gene or to affect said desired phenotype.

70. The method of claim 69 wherein the gene product is protein, the protein is purified from the cell and the test compound is exposed to the purified protein.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re: Application of

Harrington J. *et al.*

Art Unit: 1632

Application No.: 09/484,331

Examiner: R. Shukla

Filed: January 18, 2000

Atty. Docket: 0221-0003L

For: Compositions and Methods
For Non-Targeted Activation
of Endogenous Genes

**DECLARATION UNDER C.F.R. § 1.132**

Assistant Commissioner of
Patents and Trademark
Washington, D.C. 20231

Sir:

The undersigned, Youssef L. Bennani, declares and states:

1. I am Director of Medicinal Chemistry at Athersys, Inc., the subject of the attached Curriculum Vitae and author of the publications shown on the list attached thereto. I was trained as an organic chemist from 1980-1991 (PhD) and have practiced in the field of medicinal chemistry and drug discovery for the past 12 years. I have been part of and led several drug discovery programs in various therapeutic areas at some of the top biopharmaceutical and pharmaceutical companies in the world, including Ligand Pharmaceuticals and Abbott Laboratories. To date, I have been associated with and responsible for discovering 5 or more drugs, one of which is a marketed drug, while others are in various pre-clinical and clinical stages of development. On the basis of

information and facts contained in the above documents and on the basis of my professional history discussed above, I submit that I am an expert in the field of drug discovery and am qualified to speak on the skill and knowledge of the person of ordinary skill in this field.

2. I have read and understand the subject matter of the above-captioned application. I have read and understand the Office Action dated October 25, 2001, rejecting claims 62-68. It is my opinion, based on the scientific evidence and reasons set forth below and in view of my professional experience, that the methods that are the subject of the rejected claims were fully supported by the specification of the above-captioned application and could have been made and used by the person of ordinary skill in the art, as claimed, as of the filing date of September 26, 1997 (Applicants' earliest effective priority date) by routine and ordinary experimentation, using the Applicants' specification as a guide.

Written Description

3. On the issue of written description, it is my understanding that the Examiner has rejected the claims because he believes that the structure of the compound in the claims is critical to practicing the claimed methods and because the specification does not disclose the structures for compounds to be tested, i.e., that there is no "written description" for the compounds.

As I discussed with the Examiner in the interview held on April 17, 2002, the structure of compounds to be tested for activity in the drug discovery process (such as the process claimed) is not critical. Claims 62-68 contain information that can be viewed as an integral part of the drug discovery process. Drug discovery can begin with a cellular system, such as the one described in the above-mentioned claims (62-68), against which random compound libraries are screened for biological activity. It is typical and routine for such screening efforts to encompass large numbers of compounds (in the ten-hundred thousands or millions) in order to maximize hit rates. It is extremely difficult and highly discouraged to pre-select for compounds in such cell-based assays. Therefore, at this stage of the drug discovery process*, compound structure is not a consideration.

*A brief description of the drug discovery process:

A) A gene is linked to a disease state by biochemical, molecular or physiological methods.

B) An in-vitro biochemical or cellular assay (functional or phenotypic) in which such a gene is activated is established.

C) The protein or the cellular system/assay is treated with a compound library containing hundreds to millions of chemical entities (small molecules, peptides, natural products, natural proteins etc.) of wide structural diversity.

D) The ability of any of these chemical entities to perturb (activate or inhibit the protein of interest) in such an assay is determined by physical-chemical methods.

E) The identity of such chemical entities or hits is determined.

F) Such hits are further evaluated for their ability to provide benefit in an in-vivo model of disease and further improved upon based on the resulting data.

G) Additional chemical modification results/should result in chemical entities with acceptable drug parameters (target selectivity, oral bio-availability, efficacy and safety).

H) Such a chemical entity is advanced into human clinical trials.

Enablement

4. On page 7 of the Office Action, the Examiner states that the person of ordinary skill in the art could not determine whether a compound that was isolated by the claimed screening method would have any of the properties of a drug. It is not clear to me why the Examiner believes this. I do not agree with this because such chemical entity, once isolated, constitutes a conventional focal point of the drug discovery process. Such a compound typically contains physical-chemical drug features that may or may not need to be further ameliorated in order to meet all the drug criteria (target selectivity, oral bio-availability, efficacy, good therapeutic index, manufacturing feasibility etc.). It is typical and routine to perform these determinations. Drawing from personal experience I have been involved in several projects that started with a high throughput-screening

program. This allowed the identification of hits, some of which had good drug-like properties that were further modified to become chemical entities with profiles acceptable for clinical drug development. A large majority of drugs, in clinical practice today, have been discovered following a path similar to the drug discovery path described above. This is common practice in our industry.

5. In the paragraph spanning pages 7 and 8 of the Office Action the Examiner states that the person of ordinary skill in the art would not know how to use the claimed method because the specification only discloses that the RAGE-activated cells can be used for drug discovery and that "drug discovery" alone would not convey the specific steps in the claims, particularly steps d and e of claim 62 and step d of claim 63. From this position the Examiner then concludes that the person of ordinary skill in the art would not be able to practice the claimed methods. I do not agree.

In my experience and opinion, the person of ordinary skill in the art (i.e., drug discovery) would immediately recognize the claimed method in the term "drug discovery" and would know how to use the RAGE-activated cells for drug discovery, including the well-known and fundamental steps used in such research field. As mentioned above, a cell-based assay is an integral part of the drug discovery process known to the person of ordinary skill in the art. This assay would be known to necessarily include the steps of treating the cell with a test compound (step C above) and

determining the effect of the test compound on the target (step D above). Therefore, it is my opinion that the artisan would know how to use the RAGE-activated cells for all the steps in the claimed process.

6. In summary, I base my opinions and conclusions on the following:

**a**. RAGE-activated cells expressing a protein or other phenotype of interest can constitute the first step in the drug discovery process.

**b**. Cell-based assays are routinely used to randomly screen for compounds, off the shelf, from compound collection libraries, or combinatorial libraries with biochemical or biological activities.

**c**. Once such compounds are discovered, further chemical modification helps address the various criteria that make up a drug such as: good solubility, good absorption, good tissue distribution, good bio-availability, selectivity and efficacy in the disease of interest as well as good and acceptable safety index.

**d**. The term "drug discovery" conveys the steps of treating a cell with a compound and determining the effect of the compound

Y. Bennani
Youssef L. Bennani, Ph. D.

4/24/02
Date

APPENDIX C



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re: Application of

Harrington J. *et al.*

Art Unit: 1632

Application No.: 09/484,331

Examiner: R. Shukla

Filed: January 18, 2000

Atty. Docket: 0221-0003L

For: Compositions and Methods
For Non-Targeted Activation
of Endogenous Genes

**DECLARATION UNDER 37 C.F.R. § 1.132**

Assistant Commissioner of
Patents and Trademark
Washington, D.C. 20231

Sir:

The undersigned, Dale S. Dhanoa, Ph.D., declares and states:

I am currently Senior Vice President of Research and Discovery at Predix Pharmaceuticals, Inc. in Woburn, Massachusetts. I submit that I specialize in the fields of drug discovery, design, synthesis, biological and pharmacological characterization of molecules (both non-peptide and peptide) for drug development, high throughput screening, binding assays, functional assays, cell-based assays, medicinal chemistry, combinatorial chemistry, and computational chemistry, as evidenced by my attached resume and the publication list. See, in particular, the short list of references 1-20 attached to this Declaration. Based on my knowledge and experience, I believe I am

qualified to speak to the skill and understanding of the person of ordinary skill in the art of drug discovery.

I have read U.S. Patent Application No. 09/941,223, filed September 26, 1997, in its entirety. I have noted the sections that specifically mention the drug discovery process. These include page 5, last paragraph; page 9, fourth full paragraph; page 12, last paragraph; page 16, first and second full paragraphs; and page 45, third full paragraph. However, I have read the entire application to put the reference to drug discovery in the context of the entire technology in the application. I have also read claims 62-69 (see copy attached).

From the entire application, I understand the technology as introducing a vector into the genome of a cell by random integration and activating one or more genes in that cell by means of a transcriptional regulatory sequence, such as a promoter, on the vector. This means that the methods can be used to randomly activate genes and cells can be produced that express a gene of interest or acquire a phenotype of interest from activation by the vector. I refer to the technology as the "RAGE" technology. To me this covers methods of activation and products of activation, such as RAGE-activated cells and gene products from RAGE-activated cells.

With respect to the time period in which my statements apply, my frame of reference would be, at the earliest, the time of September 26, 1997. This is the time that the patent application that I have reviewed was filed. I have refreshed my memory as to

my understanding of the state of art of drug discovery on and about that time by recalling the projects I worked on, the scientific literature and conferences, my publications and presentations, as well as my personal notes and mementos from that time period. See my resume, attached.

The issue, as I understand it, is that the Patent Examiner believes that the application fails to convey, to the person of ordinary skill in the field of drug discovery, the step of screening a test compound on a RAGE-activated cell.

I do not agree with this position for the reasons that follow.

Drug Discovery: Summary Introduction

The drug discovery process, at a minimum, involved screening a test compound for a desired effect on a gene product or on a phenotype.

It was understood that drug discovery needed an end point to assess qualitatively or quantitatively the effect of a compound or compounds on the activation or inactivation (stimulation or agonist activity measurement or inhibition or antagonist activity measurement, respectively) of functional activity of a protein in a cell. Typically, two approaches were most commonly used: protein-based screening (included cell lysate, membrane-bound or fully/partially purified protein) and cell-based screening.

Generally, protein-based screening was utilized for determining the binding affinity of compounds against the target protein (for example, G protein-coupled receptors) or inhibitory potency (percent inhibition) against soluble protein (for example, HIV protease).

Protein-based assay measures the binding affinity of compounds with the protein but not its functional activity, meaning whether it will block or activate the biological function (response) of the target protein. These *in vitro* assays alone, however, would not demonstrate functional activity in cells expressing target protein or directly test its efficacy in animals.

Hence, besides determining the *in vitro* activities, these compounds would have been tested in whole cell assays. Whole cell assays were actually a better measure of the performance of test compounds if one was testing for the effect of the compound on a cellular process. In fact, screening compounds directly in cell-based assays was a more efficient process.

Cell-based assays can directly give the compound's functional activity against a protein or proteins. This approach is one step closer to the target and can bypass the protein isolation/purification. Cell-based assays will give somewhat qualitative measure of a compound's biological activity.

Drug Discovery: Detailed Explanation

Any potential drug must demonstrate efficacy in cells, tissues, or animals in its preclinical research and ultimately in humans. During the lead discovery and optimization of drug development candidates, knowing the structure-activity data of drug candidates is extremely essential. This is acquired by a number of ways: protein-ligand binding affinity and/or biological activity measured by cell-based assays.

These data may be generated by screening compounds against a target by using the protein and/or cell-based assays. Even if the affinity of a particular compound (hit/lead/drug) is already determined against a target protein, it is then tested in cells (or tissues) expressing the target protein to determine its functional activity in a biological system. This screen could also be used as a primary screen as well to identify initial active compounds (aka hit/lead). The cell-based approach is one of the most important methods available over the last several decades that has been driving drug discovery forward by providing this invaluable information for potential drug property optimization including its potency, specificity, functional activity, toxicity and cell-penetration.

Cell-based assay is a term used to refer to a number of different experiments using living cells. The general definition can include a variety of assays that measure cell proliferation, functional activity, toxicity, and motility. Cell-based assays differ from screening against proteins (enzymes, receptors, kinases) or antibody-based assays.

*Cell-based assays provided a more accurate representation of the real-life model since living cells are used.*

Cell functions are an aggregate of many interacting signaling and feedback biological pathways. Compound screening using isolated protein targets cannot consider this complexity. Thus, testing of compounds (drug leads and/or drug candidates and/or drugs) in whole cells provided a much more complete understanding of the effects of the compounds as potential drugs. The advantages of employing cell based assays for compound screening included:

- Efficacy determination by measuring function and biological behavior in cells
- Evaluation of molecular interactions within the inside environment of the cells
- Evaluation of drug penetration at early stages in whole cells
- Evaluation of compound toxicity and non-specific effects on cells
- Identification of orphan targets whose function and identity is unknown require cell-based functional assays
- No protein purification and isolation required
- Powerful in identifying false-positives earlier in drug discovery, unlike protein-based assays

Cell-based assays were used in addition to (not in lieu of) protein-based screening assays for compound screening and it was a necessity for screening selected (or all) compounds to eliminate false-positives and identify potential drug candidates. *It was not a matter of either protein-based or cell-based assays, but instead both these approaches were routinely used in drug discovery.* Moreover, cell-based assays were more essential

than protein-based assays for drug screening and drug-profiling as cell-based screens were better representatives of the *in vivo* biological systems to evaluate fate of compounds as drugs.

Selected examples out of several successful drug discovery programs, carried out on or before September 26, 1997, where both cell-based assays and protein-based assays have been used include:

- Angiotensin II receptor antagonist drug, Cozaar (Losartan) for treating hypertension
- Endothelin receptor antagonist drug, Tracleer (Bosentan) for treating acute pulmonary hypertension
- HIV Protease inhibitor drug, Crixivan, for AIDS
- Neurokinin receptor antagonist drug, Emend, for treating emesis
- Corticotrophin Releasing Hormone Receptor antagonists for the potential treatment of stress related diseases, including anxiety and depression etc.

Protein-based screening identified binders (ligands/compounds) and needed cell-based assays, as well as animal studies, to identify potential drugs, while cell-based assays identified entities that are not only biologically active in *ex-vivo* testing, but have a much greater chance of being active in *in vivo* also.

## The Patent Application

The application in several places, as I indicated above, refers to the use of the RAGE technology in drug discovery. Because the state of the art of drug discovery, as

described above, at the application's filing date of September 26, 1997, the cited passages, within the full context of the application, would have indicated to me that a compound could be tested against a RAGE cell with an activated gene of interest to determine if the compound affects the gene of interest or phenotype of interest.

The patent application refers to using the purified protein for drug discovery. (See the application page 5, last paragraph; page 16, lines 12-13; page 12, last paragraph.) As stated above, this was typically done when the test was for a compound that binds to the protein. However, this was not a necessary step. Often, especially in preliminary drug discovery, it was undesirable to go through the steps of actually purifying a specific protein. Therefore, compounds would have been tested in cellular lysates or against whole cells. This would have been a highly preferred way to do initial compound testing. In fact, for assessing the effect on a cellular process, a whole cell assay was the only way.

The application also indicates that cells can be cultured *in vitro* and used for drug discovery. (See the application, page 9, lines 12-15; page 45, lines 22-25.) This means to me that the RAGE cell with the activated gene is exposed to a test compound and then the effect of the compound is assessed.

I also believe that a person of ordinary skill in the field, having read the application, would have realized that what is intended by the application is to expose a test compound to a gene product both by way of a protein product *in vitro* (as explicitly stated) and also by way of a whole cell assay (as clearly implied).

Based on my reading of the patent application, therefore, it is my opinion that the person of ordinary skill in the field of drug discovery, reading this application on or about the filing date of September 26, 1997, would have realized that the Applicants, by mentioning the drug discovery process as they did, implicitly were describing the drug discovery method in claims 62-69, copy attached.

Dale S. Dhanoa

Dale S. Dhanoa, Ph.D.

July 10, 2003

Date